Remarks

Claims 1-4, 7-10, 12-16, 18, 20, 21, and 23-29 are pending in the application. Claims 5, 6, 11, 17, 19, and 22 were canceled without prejudice. Claims 1, 18, 20, 21, and 23-25 were amended. Support for the claim amendments can be found throughout the application. Therefore, no new matter has been added. Importantly, the claim amendments should not be construed to be an acquiescence to any of the claim rejections. Rather, the amendments to the claims are being made solely to expedite the prosecution of the above-identified application. The Applicants expressly reserve the right to further prosecute the same or similar claims in subsequent patent applications claiming the benefit of priority to the instant application. 35 USC § 120.

Claim Rejections Based on 35 USC § 112¶1

Claims 1-29 were rejected under 35 USC § 112¶1, based on the Examiner's contention that they do "not provide enablement for multitudes of compounds falling under the generic formula **A** in a variety of claimed carriers." In order to expedite prosecution, claim 1 has been amended to include compounds of formula **A** bearing closer structurally similarity to fentanyl. The compounds of the amended claim can be prepared by known procedures or by simple modifications therof, which would be known to one of ordinary skill in the art. Claims 18, 20, 21, and 23-25 were amended to reflect the changes made to claim 1. Claims 5, 6, 11, 17, 19, and 22 were canceled because they were redundant in light of the amendments to claims 1, 18, 20, 21, and 23-25. Accordingly, the Applicants respectfully request the withdrawal of the rejections of claims 1-4, 7-10, 12-16, 18, 20, 21, and 23-29 under 35 USC § 112¶1.

Claim Rejections Based on 35 USC § 102(b)

Various sets of claims were rejected under 35 USC 102(b), based on the Examiner's contentions that they are anticipated by various patents and publications. To better organize the Applicant's traverses of the Examiner's rejections under 35 USC 102(b), they are set forth below in paragraphs numbered corresponding to the numbering scheme used in the Office Action.

4. Claims 1-26, and 28 were rejected under 35 USC § 102(b), based on the Examiner's contention that they are anticipated by WO 92/02256. Specifically, the Examiner contends that the reference "discloses cyclodextrin complexes containing fentanyl, alfentanil, sufentanil, and lofentanil for the treatment of pain." The Applicants respectfully traverse the Examiner's rejections.

The Applicants respectfully assert that the WO 92/02256 reference does not anticipate the rejected claims because it does not provide examples for compounds that are within of the scope of the amended claims. The Applicants point out that the WO 92/02256 reference does not give any examples of using fentanyl, and the Examiner is reminded that a mere allusion to the possibility of using fentanyl in combination with a cyclodextrin, e.g., claim 16 of WO 92/02256, does not constitute the basis of rejection under 35 USC 102(b). Futher, the Applicants respectfully remind the Examiner that "a claim is anticipated only if each and every element as set forth in the claim, either expressed or inherently described, is found in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Applying this standard, the Applicants respectfully assert that the WO 92/02256 reference does not anticipate amended independent claim 1 or any subsequent dependent claims. Accordingly, the Applicants respectfully request the withdrawal of the rejections of claims 1-4, 7-10, 12-16, 18, 20, 21, and 23-26, and 28 under 35 USC 102(b) based on the WO 92/02256 reference.

5. Claims 1, 3-26, and 28-29 were rejected under 35 USC § 102(b), based on the Examiner's contention that they are anticipated by Mikhailova (XP 002208225). Specifically, the Examiner contends that the reference "discloses liposomal formulations containing fentanyl for the treatment of pain in humans." In order to expedite prosecution, claim 1 has been amended to remove liposomes from the Markush group defining the excipient claim limitation. Accordingly, the Applicants respectfully request the withdrawal of the rejections of claims 1, 3, 4, 7-10, 12-16, 18, 20, 21, and 23-26, and 28-29 under 35 USC 102(b) based on Mikhailova (XP 002208225).

6. Claims 1, 3-26, and 28 were rejected under 35 USC § 102(b), based on the Examiner's contention that they are anticipated by U.S. Pat. No. 5,451,408 ("the '408 patent"). Specifically, the Examiner contends that the reference "discloses liposomal formulations containing fentanyl for the treatment of pain." As noted above, in order to expedite prosecution, claim 1 has been

amended to remove liposomes from the Markush group defining the excipient claim limitation. Accordingly, the Applicants respectfully request the withdrawal of the rejections of claims 1, 3, 4, 7-10, 12-16, 18, 20, 21, and 23-26, and 28 under 35 USC 102(b) based on the '408 patent.

Claim Rejections Based on 35 USC § 103(a)

Various sets of claims were rejected under 35 USC 103(a), based on the Examiner's contentions that they are unpatentable over various patents and publications. To better organize the Applicant's traverses of the Examiner's rejections under 35 USC 103(a), they are set forth below in paragraphs numbered corresponding to the numbering scheme used in the Office Action.

8. Claims 1, 3-29 were rejected under 35 USC 103(a), based on the Examiner's contention that they are unpatentable over Mikhailova (XP 002208225) or U.S. Pat. No. 5,451,408 ("the '408 patent"). Specificially, the Examiner contends that "it is deemed obvious to one of ordinary skill in the art to encapsulate any compound based on the basic structure of fentanyl in the liposomes of Michailova and Mezei with a reasonable expectation of success" and that "it is reasonable to expect that the compositions which is effective in humans would be effective in animals since animal experiments are often extrapolated to humans." The Applicants respectfully assert that the teachings of Mikhailova and the '408 patent do not render obvious the amended claims because their teachings are limited to the use of liposomes as excipient; whereas, the Markush group defining the excipient in amended claim 1 does not include liposomes. Therefore, the Applicants respectfully contend that the Examiner has failed to establish the required *prima facie* showing of obviousness for the rejected claims. Accordingly, the Applicants respectfully request the withdrawal of the claims rejection under 35 USC § 103(a) based on Mikhailova (XP 002208225) or the '408 patent.

9. Claims 1-29 were rejected under 35 USC 103(a), based on the Examiner's contention that they are unpatentable over WO 92/02256. Specificially, the Examiner contends that "it is deemed obvious to one of ordinary skill in the art to encapsulate any compound based on the basic structure of fentanyl in the cyclodextrin compositions of WO with a reasonable expectation of success" and that "it is reasonable to expect that the compositions which are effective in

humans would be effective in rats would be effective in other animals and humans too." The Applicants respectfully traverse the Examiner's rejections.

The Applicants respectfully contend that the WO 92/02256 reference, prior to the Applicants' invention, would not have led one of ordinary skill in the art to believe they would have a reasonable expectation of success in a program focused on developing a formulation for the treatment of pain, comprising cyclodextrins and fentanyl or similar structural analogs thereof. *See In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). The Applicants respectfully remind the Examiner that no examples using fentanyl are provided in WO 92/02256. Furthermore, the examples in WO 92/02256 indicate that the molecules tested, e.g., morphine and lofentanil, possessed significant differences in biological activity, thereby illustrating that relatively-modest changes in structural features of the constituent small molecule have a significant impact on the biological activity of the formulation in treatment of pain. Hence, armed only with the teachings of WO 92/02256, the Applicants respectfully contend that one of ordinary skill in the art would not have had a reasonable expectation of success in a program directed toward the development of orally-bioavailable formulations of the compounds defined in the claims. Accordingly, the Applicants respectfully request the withdrawal of the claims rejection under 35 USC § 103(a) based on the WO 92/02256 reference.

Fees

The Applicants believe no fee is due in connection with the filing of this paper. Nevertheless, the Director is hereby authorized to charge any required fee to our Deposit Account, **06-1448**.

Conclusion

In view of the above amendments and remarks, it is believed that the pending claims are in condition for allowance. The Applicants respectfully request reconsideration and withdrawal of the pending rejections. The Applicants thank the Examiner for careful consideration of the present case. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to contact the undersigned.

Respectfully submitted,
FOLEY HOAG LLP

Dana Gordon

Dana M. Gordon, Ph.D.
Registration No. 44,719
Attorney for Applicants

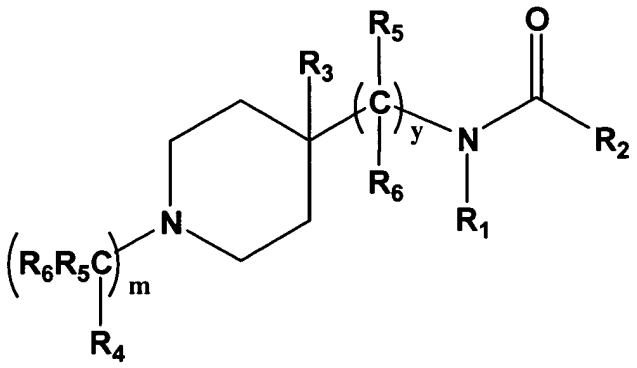
Patent Group
FOLEY HOAG LLP
155 Seaport Boulevard
Boston, MA 02210

(617) 832-1000
(617) 832-7000 (FAX)

Date: 5/29/03

Marked-up Version of Amended Claims Showing Changes Made

1. (**amended**) A formulation, comprising: an excipient selected from the group consisting of cyclodextrins, [liposomes,] micelle forming agents, and polymeric carriers; and a compound represented by **A**:



A

wherein

m is 0, 1, 2, 3 or 4;

y is 0[, 1, or 2];

R_1 represents [alkyl, cycloalkyl,] aryl[,] or heteroaryl[, aralkyl, or heteroaralkyl];

R_2 represents H, alkyl, or cycloalkyl[, aryl, heteroaryl, aralkyl, or heteroaralkyl];

R_3 represents H, alkyl, aryl, heteroaryl, [OR_2, $OC(O)R_2$,] CH_2OR_2, or CO_2R_2;

R_4 represents [H, alkyl, cycloalkyl, alkenyl, cycloalkenyl,] aryl[, or heteroaryl];

R_5 represents independently for each occurrence H, alkyl, or cycloalkyl[, aryl, heteroaryl, F, OR_2, or $OC(O)R_2$];

R_6 represents independently for each occurrence H, alkyl, or cycloalkyl[, aryl, heteroaryl, F, OR_2, or $OC(O)R_2$];

any two geminal or vicinal instances of R_5 and R_6 may be connected through a covalent bond; and

the stereochemical configuration at any stereocenter of a compound represented by **A** is *R, S*, or a mixture of these configurations.

18. (**amended**) The formulation of claim 1, wherein m is 2[; y is 0;] and R_1 represents aryl.

20. (**amended**) The formulation of claim 1, wherein m is 2; [y is 0;] R_1 represents aryl; and R_2 represents independently for each occurrence alkyl.

21. (**amended**) The formulation of claim 1, wherein m is 2; [y is 0;] R_1 represents aryl; R_2 represents independently for each occurrence alkyl; and R_3 represents H.

23. (**amended**) The formulation of claim 1, wherein m is 2; [y is 0;] R_1 represents aryl; R_2 represents independently for each occurrence alkyl; R_3 represents H; [R_4 represents aryl;] and R_5 represents independently for each occurrence H.

24. (**amended**) The formulation of claim 1, wherein m is 2; [y is 0;] R_1 represents aryl; R_2 represents independently for each occurrence alkyl; R_3 represents H; [R_4 represents aryl;] R_5 represents independently for each occurrence H; and R_6 represents independently for each occurrence H.

25. (**amended**) The formulation of claim 1, wherein m is 2; [y is 0;] R_1 represents phenyl; R_2 represents independently for each occurrence ethyl; R_3 represents H; R_4 represents phenyl; R_5 represents independently for each occurrence H; and R_6 represents independently for each occurrence H.